Answer 1:

Bibliographic Information

Dasatinib (BMS-354825) Pharmacokinetics and Pharmacodynamic Biomarkers in Animal Models Predict Optimal Clinical Exposure. Luo, Feng R.; Yang, Zheng; Camuso, Amy; Smykla, Richard; McGlinchey, Kelly; Fager, Krista; Flefleh, Christine; Castaneda, Stephen; Inigo, Ivan; Kan, David; Wen, Mei-Li; Kramer, Robert; Blackwood-Chirchir, Anne; Lee, Francis Y. Pharmaceutical Research Institute, Bristol-Myers Squibb Company, Princeton, NJ, USA. Clinical Cancer Research (2006), 12(23), 7180-7186. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:197926 AN 2006:1264188 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Chronic myeloid leukemia (CML) is caused by reciprocal translocation between chromosomes 9 and 22, forming BCR-ABL, a constitutively activated tyrosine kinase. Imatinib mesylate, a selective inhibitor of BCR-ABL, represents current frontline therapy for CML; however, emerging evidence suggests that drug resistance to imatinib may limit its long-term success. To improve treatment options, dasatinib (BMS-354825) was developed as a novel, oral, multi-targeted kinase inhibitor of BCR-ABL and SRC family kinases. To date, dasatinib has shown promising anti-leukemic activity in preclin. models of CML and in phase I/II clin. studies in patients with imatinib-resistant or imatinib-intolerant disease. Exptl. Design: The pharmacokinetic and pharmacodynamic biomarkers of dasatinib were investigated in K562 human CML xenografts grown s.c. in severe combined immunodeficient mice. Tumoral levels of phospho-BCR-ABL/phospho-CrkL were detd. by Western blot. Results: Following a single oral administration of dasatinib at a preclin. efficacious dose of 1.25 or 2.5 mg/kg, tumoral phospho-BCR-ABL/phospho-CrkL were maximally inhibited at .apprx.3 h and recovered to basal levels by 24 h. The time course and extent of the inhibition correlated with the plasma levels of dasatinib in mice. Pharmacokinetic/biomarker modeling predicted that the plasma concn. of dasatinib required to inhibit 90% of phospho-BCR-ABL in vivo was 10.9 ng/mL in mice and 14.6 ng/mL in humans, which is within the range of concns. achieved in CML patients who responded to dasatinib treatment in the clinic. Conclusions: Phospho-BCR-ABL/phospho-CrkL are likely to be useful clin. biomarkers for the assessment of BCR-ABL kinase inhibition by dasatinib.

Answer 2:

Bibliographic Information

Action of the Src Family Kinase Inhibitor, Dasatinib (BMS-354825), on Human Prostate Cancer Cells. Nam, Sangkil; Kim, Donghwa; Cheng, Jin Q.; Zhang, Shumin; Lee, Ji-Hyun; Buettner, Ralf; Mirosevich, Janni; Lee, Francis Y.; Jove, Richard. Molecular Oncology Program, University of South Florida College of Medicine, Tampa, FL, USA. Cancer Research (2005), 65(20), 9185-9189. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 143:379294 AN 2005:1115906 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Src family kinases (SFK) are currently being investigated as targets for treatment strategies in various cancers. The novel SFK/Abl inhibitor, dasatinib (BMS-354825), is a promising therapeutic agent with oral bioavailability. Dasatinib has been shown to inhibit growth of Bcr-Abl-dependent chronic myeloid leukemia xenografts in nude mice. Dasatinib also has been shown to have activity against cultured human prostate and breast cancer cells. However, the mol. mechanism by which dasatinib acts on epithelial tumor cells remains unknown. In this study, we show that dasatinib blocks the kinase activities of the SFKs, Lyn, and Src, in human prostate cancer cells at low nanomolar concns. Moreover, focal adhesion kinase and Crk-assocd. substrate (p130CAS) signaling downstream of SFKs are also inhibited at similar concns. of dasatinib. Consistent with inhibition of these signaling pathways, dasatinib suppresses cell adhesion, migration, and invasion of prostate cancer cells at low nanomolar concns. Therefore, dasatinib has potential as a therapeutic agent for metastatic prostate cancers harboring activated SFK and focal adhesion kinase signaling.

Answer 3:

Bibliographic Information

Dasatinib: BMS 354825. Anonymous Drugs in R&D (2006), 7(2), 129-32. Journal code: 100883647. ISSN:1174-5886. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16542059 AN 2006153564 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Dasatinib [BMS 354825] is an orally active, small molecule, dual inhibitor of both SRC and ABL kinases that is under development with Bristol-Myers Squibb for the treatment of patients with chronic myelogenous leukaemia (CML) and imatinib-acquired resistance/intolerance. While imatinib remains a frontline therapy for CML, patients with advanced disease frequently develop resistance to imatinib therapy through multiple mechanisms. These mechanisms include insufficient potency at therapeutic doses, activation of alternate oncogenic pathways, and overexpression of the multidrug-resistant gene. One of the possible causes of imatinib-acquired resistance is associated with increased expression of the SRC-related kinase Lyn and loss of BCR-ABL dependence arising from sequence mutations. In December 2005, Bristol-Myers Squibb announced that it has completed the rolling NDA submission to the US FDA for dasatinib in the treatment of CML in chronic, accelerated or blast phases, as well as Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (ALL) in patients with resistance or intolerance to prior treatment. At the Bristol-Myers Squibb R&D Day in May 2005, the company stated that it plans to evaluate dasatinib in solid tumours. In in vitro assays, dasatinib induced apoptosis and had potent activity in the imatinib-resistant tumour cells lines and CML patient specimens. It effectively inhibited the proliferation of cells expressing nearly all imatinib-resistant isoforms. In vivo, dasatinib has shown efficacy, with no apparent toxicity, when administered orally in SCID mice with xenografts of imatinib-sensitive and resistant human CML cells lines. Dasatinib is also undergoing preclinical evaluation for its potential as a therapy against multiple myeloma. Bristol-Myers Squibb has a composition-of-matter patent covering this research approach that will expire in 2020.